REPORT DOCUMENTATION PAGE

Form Approved OMB NO. 0704-0188

1. REPORT DATE (DD-MM-YYYY)	2. REPORT TYPE	3. DATES COVERED (From - To)
28-02-2017	Final Report	1-Dec-2013 - 30-Nov-2016

4. TITLE AND SUBTITLE
Final Report: Modeling Subconscious Vision

5a. CONTRACT NUMBER
W911NF-13-1-0449

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER
611102

6. AUTHORS
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAMES AND ADDRESSES
University of Michigan - Ann Arbor
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS (ES)
U.S. Army Research Office
P.O. Box 12211
Research Triangle Park, NC 27709-2211

10. SPONSOR/MONITOR'S ACRONYM(S)
ARO

11. SPONSOR/MONITOR'S REPORT NUMBER(S)
64618-MA.6

12. DISTRIBUTION AVAILIBILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES
The views, opinions and/or findings contained in this report are those of the author(s) and should not contrued as an official Department of the Army position, policy or decision, unless so designated by other documentation.

14. ABSTRACT
This grant supported work exploring subconscious vision through mathematical modeling. Mathematical modeling has had a tremendous impact on our understanding of conscious vision. Recently, a separate subconscious visual system was discovered in the retina, mediated by intrinsically photosensitive retinal ganglion cells (ipRGCs) which can function in the absence of rods and cones. We used mathematics to classify the responses of ipRGCs and developed mathematical models of their electrical activity. We then developed numerical methods that allowed for a large scale simulation of the entire retina. Studying a target of ipRGCs, the suprachiasmatic nucleus (SCN), which

15. SUBJECT TERMS
mathematical modeling, subconscious vision, ipRGC, computational neuroscience, biomathematics

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	15. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			Daniel Forger
UU	UU	UU	UU		19b. TELEPHONE NUMBER 734-763-4544

Report Title

Final Report: Modeling Subconscious Vision

ABSTRACT

This grant supported work exploring subconscious vision through mathematical modeling. Mathematical modeling has had a tremendous impact on our understanding of conscious vision. Recently, a separate subconscious visual system was discovered in the retina, mediated by intrinsically photosensitive retinal ganglion cells (ipRGCs) which can function in the absence of rods and cones. We used mathematics to classify the responses of ipRGCs and developed mathematical models of their electrical activity. We then developed numerical methods that allowed for a large scale simulation of the entire retina. Studying a target of ipRGCs, the suprachiasmatic nucleus (SCN), which forms the central daily (circadian) clock in the brain, we showed that the SCN processes subconscious visual information to enhance visual function. Further studying the effects of light on circadian timekeeping, we developed a smartphone app, Entrain, to help adjust human circadian rhythms. This app was installed nearly 200,000 times. Data collected from the app resulted in one of the largest studies of human sleep.

Enter List of papers submitted or published that acknowledge ARO support from the start of the project to the date of this printing. List the papers, including journal references, in the following categories:

(a) Papers published in peer-reviewed journals (N/A for none)

Received		Paper
02/28/2017	3	Olivia J. Walch, L. Samantha Zhang, Aaron N. Reifler, Michael E. Dolikian, Daniel B. Forger, and Kwoon Y. Wong. Characterizing and modeling the intrinsic light response of rat ganglion-cell photoreceptors, Journal of Neurophysiology, (06 2015): 0. doi: 365,153.00
02/28/2017	5	Olivia J. Walch, Marisa C. Eisenberg. Parameter identifiability and identifiable combinations in generalized Hodgkin–Huxley models, Neurocomputing, ( ): 137. doi: 1,033,012.00
02/28/2017	4	O. J. Walch, A. Cochran, D. B. Forger. A global quantification of "normal" sleep schedules using smartphone data, Science Advances, ( ): . doi: 1,033,011.00
08/29/2014	2	D. DeWoskin, W. Geng, A. R. Stinchcombe, D. B. Forger. It is not the parts, but how they interact that determines the behaviour of circadian rhythms across scales and organisms, Interface Focus, (04 2014): 0. doi: 10.1098/rsfs.2013.0076 333,304.00
TOTAL:	**4**	

Number of Papers published in peer-reviewed journals:

(b) Papers published in non-peer-reviewed journals (N/A for none)

Received	Paper
TOTAL:	

Number of Papers published in non peer-reviewed journals:

(c) Presentations

Number of Presentations: 0.00

Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Received	Paper

TOTAL:

Number of Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Peer-Reviewed Conference Proceeding publications (other than abstracts):

Received	Paper

TOTAL:

Number of Peer-Reviewed Conference Proceeding publications (other than abstracts):

(d) Manuscripts

Received	Paper	
03/11/2014	1.00	DeWoskin, D, Geng, W, Stinchcombe, AR, Forger, DB. It's not the parts, but how they interact that determines the behavior of circadian rhythms across scales and organisms, Royal Society Interface Foxus (03 2014)

TOTAL: **1**

Number of Manuscripts:

Books

Received Book

TOTAL:

Received Book Chapter

TOTAL:

Patents Submitted

Patents Awarded

Awards

Graduate Students

NAME	PERCENT_SUPPORTED
FTE Equivalent:	
Total Number:	

Names of Post Doctorates

NAME	PERCENT_SUPPORTED
Adam Stinchcombe	0.00
FTE Equivalent:	**0.00**
Total Number:	**1**

Names of Faculty Supported

NAME	PERCENT_SUPPORTED	National Academy Member
Daniel Forger	0.00	
Kwoon Wong	0.00	
FTE Equivalent:	**0.00**	
Total Number:	**2**	

Names of Under Graduate students supported

NAME	PERCENT_SUPPORTED
FTE Equivalent:	
Total Number:	

Student Metrics

This section only applies to graduating undergraduates supported by this agreement in this reporting period

The number of undergraduates funded by this agreement who graduated during this period: 1.00

The number of undergraduates funded by this agreement who graduated during this period with a degree in science, mathematics, engineering, or technology fields:..... 1.00

The number of undergraduates funded by your agreement who graduated during this period and will continue to pursue a graduate or Ph.D. degree in science, mathematics, engineering, or technology fields:..... 1.00

Number of graduating undergraduates who achieved a 3.5 GPA to 4.0 (4.0 max scale):..... 1.00

Number of graduating undergraduates funded by a DoD funded Center of Excellence grant for Education, Research and Engineering:..... 0.00

The number of undergraduates funded by your agreement who graduated during this period and intend to work for the Department of Defense 0.00

The number of undergraduates funded by your agreement who graduated during this period and will receive scholarships or fellowships for further studies in science, mathematics, engineering or technology fields: 0.00

Names of Personnel receiving masters degrees

NAME
Total Number:

Names of personnel receiving PHDs

NAME	
Olivia Walch	
Total Number:	**1**

Names of other research staff

NAME	PERCENT_SUPPORTED
FTE Equivalent:	
Total Number:	

Sub Contractors (DD882)

Inventions (DD882)

Scientific Progress

See Attachment

Technology Transfer

This final report expand on our 3rd year report (which came only 3 months before the end of this grant) and our previous reports.

Major goals

Our team consists of a collaboration between Kwoon Wong's lab at the Kellogg Eye Center at the University of Michigan, and Daniel Forger's group in the mathematics department at the University of Michigan. Olivia Walch, a co-advised graduate student between Dr. Forger and Dr. Wong was supported off the grant, as was a post-doc, Adam Stinchcombe. Several members of the Wong lab collected experimental data for the collaboration. The collaboration was very successful, not only in our science, but also in career development. Olivia Walch successfully defended her dissertation, "Exploring light and subconscious vision through mathematical modeling," and now has a position as a post-doctoral researcher continuing her research. Adam Stinchcombe has just accepted a tenure-track position at the University of Toronto.

The aims of our grant are to:

Model the intrinsic photoresponse of ipRGCs (Aim 1)
Model the electrophysiology of ipRGCs (Aim 2)
Model the inputs to ipRGCs from other parts of the retina (Aim 3)
Determine what can the ipRGC network see? (Aim 4)

One measure of the progress we have made is the number of talks that we have been invited to give based on this research. These include major talks at the biannual meeting of the Society for Research on Biological Rhythms, the annual meeting of the American Professional Sleep Societies and many universities and institutes such as Walter Reed, Duke, Rensselaer and the University of Washington. Dr. Forger was very glad to have given a talk to the ARO office in the research triangle and received much valuable feedback on his work.

Aim 1: Our first published paper from this grant was:

DeWoskin D, Geng W, Stinchcombe AR, Forger DB "It is not the parts, but how they interact that determines the behaviour of circadian rhythms across scales and organisms." *Interface Focus* (2014) **4**(3):20130076.

This project set some of the groundwork for our simulations of the suprachiasmatic nucleus (SCN). The SCN is one of the major targets of subconscious vision. We used army funding to finish the publication and pay publication fees. Most importantly for us, we described how we used advanced computing to perform detailed simulations of this network.

Our results from Aim 1 have now been published in the Journal of Neurophysiology:

Walch O, Zhang L, Forger DB and Wong K "Characterizing and modeling the intrinsic light response of rat ganglion-cell photoreceptors." *J Neurophysiology* (2015) **114** 2955-2966.

In this work, the Wong lab recorded the response of ipRGCs to different light patterns and intensities. Pulses of varying durations were presented, with different times between the pulses, and the responses recorded. These were then fit to quantitative mathematical models and clustered into groups of ipRGCs.

We found that there were three significant groups of responses of ipRGCs to light. These correspond with the M1 neurons, which are important for circadian biology, the M2/M4 neurons, and the M3/M5 neurons. Differences were seen in overall shape, amplitudes and response times. Three models were fit to the three different groups. From the parameters of the models, we were able to hypothesize physiological differences between the three groups. To accurately fit the dynamics, we needed to include some details of the electrophysiology of the neurons, e.g. the fact that they enter depolarization block, but did not give an ionic description of this process.

Aim 2: As described in Aim 2, we have developed a mathematical model of the electrical activity of ipRGCs. An important mathematical question arose in the development of this model: Given experimental data on the different ionic currents that affect the electrical activity of ipRGCs, can one determine the parameters of a model that is in the standard Hodgkin-Huxley form?

Olivia Walch worked diligently on this mathematical question with Marissa Eisenberg, an expert at Michigan on model identifiability. Using techniques from differential algebra, they were able to show that most of the parameters were indeed identifiable. This was recently published:

Walch O, Eisenberg MC "Parameter identifiability and identifiable combinations in generalized Hodgkin-Huxley models" *Neurocomputing* (2016) **199** 137-143.

This information helped in the development of an electrophysiological model of an ipRGC. However, we had one additional challenge to overcome. Initially, our model was not fitting the data well. We then realized that ipRGCs are large cells where spatial dynamics may play an important role. This challenge was solved in two ways. First recordings from the Wong lab were generated from ipRGCs with their long dendrites removed. This represented a small enough neuron so that we could directly compare it to an ordinary differential equation model. Additionally, we developed a partial differential equation model of ipRGCs to account for changes in the electrical activity in space and time. We now have models of the two most important types of ipRGCs for us, M1 and M4 cells. This work will soon be submitted for publication.

Aims 3 and 4: We have a working model of the retina based on work described in Aim 3 of the grant. This model contains representations of all major parts of the retina, including rods, cones, bipolar cells, horizontal cells, amacrine cells and retinal ganglion cells. The model contains about 1,000,000 cells and utilizes special GPU hardware for fast simulation. We are currently optimizing the code so the model can be widely used.

We have been able to make more progress on Aim 4 than originally expected due to an important new unpublished dataset from the Lucas lab at the University of Manchester. These are used in simulations by Adam Stinchcombe. We were very lucky to have access to a dataset recording SCN neurons in response to visual patterns. This unique resource allowed us to measure subconscious vision in real time in a live animal. In these experiments, visual stimuli are presented to an animal, and the responses of neurons in the suprachiasmatic nuclei (SCN) are recorded. This dataset is an excellent resource especially as visual stimuli are very rich in spatiotemporal information.

To our surprise and delight, these experimental data greatly constrained the model. There are thousands of neurons in the SCN, each potentially connecting to each other. The actual mapping of connections between SCN neurons is much too difficult to determine experimentally. In fact, the mathematical inverse problem of determining coupling of neuronal networks is one of the leading problems in computational neuroscience, and an important part of the recent BRAIN government initiatives.

We found that choosing and testing the right spatiotemporal patterns could yield experimental data that would highly constrain the network connectivity. In fact, we were able to reconstruct much of the coupling structure of the network by fitting the experimentally determined responses of a small (~20) number of neurons within the network to visual stimuli. Choosing network connections randomly had a less than 1 in 10,000 chance of accurately representing the data. The network connectivity that did fit the data matched known general properties, for example that neurons tend to be coupled as small world networks.

Not only has this new method discovered how neurons in the SCN are coupled, and the coupling between ipRGCs to SCN neurons, but we believe that this method could also determine the connectivity of other brain regions, particularly those receiving input from the retina. Light could also be used to probe a neuronal network ontogenetically, which might allow future use of this method for neuronal networks not receiving input from the retina.

An additional potential publication has also spun off from this work. Our work indicates that the SCN network is highly constrained by responses to brief (< 1 second) light signals. This is very counterintuitive since the SCN is the site of the central circadian pacemaker, and thus should operate on a 24-hour timescale. Could the role of these nuclei also be to process subconscious visual information? If so,

then we will have redefined the presumptive role of this region of the brain, which has been held for forty years.

One test of this high payoff hypothesis is to find visual tasks that are enhanced by the SCN neuronal network. Testing our model against standard visual tasks, we have found that the SCN neuronal network enhances contrast adaptation, an important part of vision that allows a visual system to function accurately in both low contrast and high contrast environments. The network could also add inhibitory responses when light signals are removed. Most importantly, we connected our SCN network to a simple model controller and asked it to perform a simple visual task: to place a spot of light in the center of the visual field. We compared the result of performing this task directly from the output of ipRGCs or from the SCN network, which processes information from ipRGCs. When the controller had access to the SCN network, it was able to accomplish the task quicker, smoother and more reliably. Thus, the SCN may enhance subconscious vision.

This collaborative work was submitted to Neuron, arguably the top neuroscience journal, where it was reviewed. The editors then suggested that we submit revised manuscripts to either Current Biology or Cell Reports, two other top journals. We have already submitted one revised manuscript to Current Biology, and plan to soon submit another to Cell Reports. We are hopeful that these manuscripts will highlight the impact mathematical model can have in understanding vision.

Entrain: Our ENTRAIN app has collected data on sleep patterns from thousands of individuals in over 100 countries. We quantified sleep globally using this data and found differences in how much individuals sleep based on age, gender and the country individuals live in. Women schedule more sleep then men, and that the effects of light due to subconscious vision's effects on the circadian clock had a much greater effect on when we wake up rather than when we go to sleep. This work was published in Science Advances:

Walch OJ, Cochran A, Forger DB "A global quantification of "normal" sleep schedules using smartphone data" *Science Advances* (2016) **2** e1501705

This work received a tremendous amount of media attention including hundreds of media pieces in print, online, via radio and television. A particularly informative media piece was in Wired magazine with a title "Oh, Good Morning Sleep Science. Welcome to the 21st Century."

An sample figure from our paper is shown below. It shows the correlation between average wake time and average bed time with sleep duration across countries. This suggests that the differences between sleep duration in different countries can be explained by bed time and not wake time.